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Comparison of fluticasone propionate and sodium cromoglycate for the treatment of childhood asthma (an open parallel group study)

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Inhaled corticosteroids are highly effective in the treatment of asthma at all ages and their use in younger children is increasing. As concerns exist about the long-term systemic side-effects of high dose inhaled corticosteroids, current guidelines continue to recommend sodium cromoglycate (SCG) as first line regular medication for children with frequent symptoms. Few published studies have compared the safety and efficacy of inhaled corticosteroids with SCG in children. This study compares SCG with the new inhaled corticosteroid, fluticasone propionate (FP), which has theoretical advantages over other currently available corticosteroids due to its negligible oral bioavailability.

This was a randomized, open, multi-centre, parallel group comparison of 50 μg FP twice daily and 20 mg SCG four times daily over 8 weeks, preceded by a 2-week baseline period. Sixty-two general practices and two hospital centres enrolled 225 asthmatic children aged 4–12 years (110 received FP; 115 received SCG). Outcome measures improved in both groups, with a significant difference in favour of FP for the key variables of mean morning and evening % predicted PEFR and % of symptom-free days and nights. No significant difference was observed for FEV_1, or relief medication use. Two children taking FP and 10 children taking SCG withdrew because of adverse events.

This study showed that low dose FP was effective and superior to SCG in young children with mild–moderate asthma. Safety studies of longer duration are needed before changing the current recommendations for inhaled corticosteroid therapy.

Introduction

Inhaled corticosteroids are highly effective in the treatment of moderate and severe asthma at all ages and their use in younger children is increasing. Effects on function of the hypothalamic–pituitary–adrenal (HPA) axis can be detected when inhaled corticosteroids are given at doses of 400 μg day^{-1} (or greater) and at the moment there is little information about possible long-term systemic effects in children who start treatment with inhaled corticosteroids in infancy or the pre-school years (1–3). For these reasons, the recently published international consensus on the management of childhood asthma continues to recommend sodium cromoglycate (SCG) as the first line regular medication for children with frequent symptoms (4). The current recommendations for inhaled corticosteroid therapy are for children who fail to respond to or comply with SCG therapy, or have severe asthma. The efficacy and safety of SCG are well established and this drug will provide good asthma control in about 60% of children with frequent symptoms (5,6). There are few published studies which have compared the safety and efficacy of inhaled corticosteroids with SCG in children (7–13).

Fluticasone propionate (FP) is a new inhaled corticosteroid currently under investigation. Preliminary work indicates it is a strong agonist at the glucocorticoid receptor conferring potent topical activity (14). Oral bioavailability is negligible (<1%) (15). This is attributed to incomplete gastrointestinal absorption and virtually complete hepatic first pass metabolism to the inactive 17-β-carboxylic acid. Although currently available inhaled corticosteroids in doses up to 400 μg day^{-1} are clinically safe, some children with more severe asthma may require life

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long prophylaxis, perhaps starting in very early childhood. There is the possibility of long-term effects on bone metabolism (16) but FP, with its negligible oral bioavailability and improved safety margin, does have theoretical advantages over the currently available inhaled corticosteroids, particularly in young children. A study of short-term growth, as measured by knemometry, confirmed that FP had a significantly lower systemic effect than the clinically equivalent dose of beclomethasone dipropionate (17). Large multi-centre studies, conducted for regulatory purposes in asthmatic children, have found FP to be superior to placebo (18) and have suggested its clinical potency to be double that of beclomethasone dipropionate (19). The aim of this study was to compare the efficacy and tolerability of inhaled FP with SCG in children who had previously received only intermittent treatment with bronchodilators, and who were receiving regular inhaled medication for the first time.

Methods

TRIAL DESIGN

This was a multi-centre, open, randomized, parallel group study comprising a 2-week baseline period and an 8-week treatment period in which 20 mg SCG four times daily was compared with 50 μg FP twice daily. Asthmatic children aged 4–12 years who had previously received only intermittent bronchodilator therapy and had never been treated with inhaled SCG or an inhaled corticosteroid, but who, on clinical grounds, were being considered for regular treatment, were recruited into the baseline assessment period. The diagnosis of asthma was based on clinical history which included recurrent episodes of wheeze and cough which had responded to bronchodilator therapy. Children who had received oral corticosteroids in the previous 6 weeks or who had been given more than three short courses of systemic corticosteroid therapy in the previous 6 months were not included. Children who had suffered a respiratory tract infection in the preceding 2 weeks were also excluded.

Before commencement of the baseline assessment, forced expiratory volume in 1 s (FEV_1) was recorded by spirometry. Peak expiratory flow rate (PEFR) was measured with a mini-Wright peak-flow meter after inhalation of 400 μg of salbutamol, in order to establish the maximum achievable PEFR. Children were taught to use the mini-Wright peak-flow meter and were only included in the study if they could demonstrate its correct use. Each child was given the appropriate meter according to age and baseline peak-flow (either a standard or low reading meter). They were asked to record the best of three blows each morning and evening and use the same meter throughout the trial. Current bronchodilator medication was replaced by salbutamol administered by the Rotahaler™ device to be taken as required. Eligibility for the treatment period was determined during the 2-week baseline period. Symptoms of cough, wheeze, disturbance of sleep or daytime activity, morning and evening PEFR and use of relief medication were recorded daily on diary cards at home. Children entered the treatment period if, on at least 7 days of the baseline period, they had reported asthma symptoms requiring one or more doses of inhaled salbutamol, or had recorded morning PEFRs of less than 80% of their maximum.

The children who fulfilled the entry criteria were then randomly allocated to receive either 20 mg SCG four times daily by capsule powder device, or 50 μg FP twice daily by Diskhaler™ device. Randomization was in balanced blocks of six, with each centre allocated at least one block.

The children continued to take 200–400 μg salbutamol by Rotahaler for symptomatic relief. They and their parents continued to make recordings on diary cards at home as in the baseline period. Each child was reviewed after 2 weeks, 5 weeks and on completion of the 8 weeks' treatment. At each visit, the diary card was collected and replaced with a new one. Inhaler techniques were checked.

The oropharynx was examined and swabs taken if clinically indicated. FEV_1 was measured by spirometry. Compliance with treatment was assessed by discussion with parents and from medication records in the patients' diary cards. Adverse events and concomitant illness were documented.

The protocol used was designed by the authors. The study was conducted by the Clinical Research Department of Allen & Hanburys Limited, through the collaboration of their Clinical Research Scientists and the participating physicians. As the intention was to recruit children who had never received regular medication, the trial was almost entirely based in general practices. The results and statistical analysis were independently reviewed by the Department of Applied Statistics at Reading University and by the authors.

The study was approved by the Ethics Committee of each participating centre, and written informed consent to participate in the study was obtained from the parent or legal guardian of each child. The study was conducted in accordance with the Declaration of Helsinki (as revised in Hong Kong, 1989), and with Good Clinical Practice guidelines as issued by the European Community (1990).

STATISTICAL ANALYSIS

The primary variable for comparing the efficacy of treatments was the change (from baseline) in mean morning % predicted PEFR at 0–2, 2–5, and 5–8 weeks' treatment. If the smallest mean difference in change of % predicted PEFR of clinical relevance between the groups is 5%, then assuming a SD common to both groups of 11% of predicted and 5% two-tailed significance, approximately 100 evaluable patients were required in each treatment group for a test at 90% power. PEFR data were expressed as the percentage of the patients' predicted values related to height (20) and were analysed by multi-variate analysis of variance. For the secondary variables, change from baseline FEV_1 (expressed as % predicted) at the end of the treatment period was compared between the treatment groups using the student's *t*-test; the percentage of days and nights on which the children were symptom-free and the frequency of use of relief medication were derived from the diary cards, and *z*-tests, i.e. using the normal distribution, were used to compare treatments at each time point. The student's *t*-test was used to test for differences between the two treatment groups in mean % predicted morning PEFR at baseline. The level of significance for all analyses was taken to be $P<0{\cdot}05$. Confidence intervals were calculated at the 95% level.

Results

Three hundred and five asthmatic children were recruited from 62 general practices and 2 hospital centres. Two hundred and twenty-five of them fulfilled the baseline entry criteria and entered the treatment period. One hundred and fifteen received SCG and 110 received FP. Although none had received regular medication, many were experiencing frequent symptoms but there were no obvious demographic differences nor statistically significant differences in asthma severity between the two treatment groups (Table 1).

There was a significant difference in morning PEFR in favour of FP during the treatment period. Multi-variate analysis of variance showed that the treatment difference changed over time, increasing to 7·5% of predicted at 6–8 weeks ($P=0{\cdot}0001$). At this time, the 95% confidence interval showed that the true difference in favour of FP was likely to be at least 3·8% and could be as much as 11·2% of predicted. The difference for evening PEFR also favoured FP but only in the latter part of the treatment period, reaching a maximum of 5·6% of predicted during the last 2 weeks. The 95% confidence interval was 2·3–9·0% of predicted; $P=0{\cdot}0011$ at 6–8 weeks (Fig. 1).

In both groups, FEV_1 improved during treatment. With FP, mean % predicted FEV_1 increased from

Table 1 Baseline patient data

	Fluticasone propionate	Sodium cromoglycate
Number	110	115
Male	64	66
Female	46	49
Age (years) Mean	8·5	7·9
Range	4·1–12·7	4·1–12·9
Proportion of:		
Symptom-free days (median)	0·14	0·15
Symptom-free nights (median)	0·46	0·46
Relief medication:		
Mean doses day^{-1} (SD)	1·97 (1·37)	1·91 (1·25)
Mean doses $night^{-1}$ (SD)	0·50 (0·53)	0·61 (0·62)
PEFR (mean % predicted)		
Morning (SD)	93·1 (21·6)	89·9 (20·6)
Evening (SD)	97·6 (23·5)	93·1 (21·3)
FEV_1 (mean % predicted) (SD)	79 1 (16·3)	77·8 (16·7)

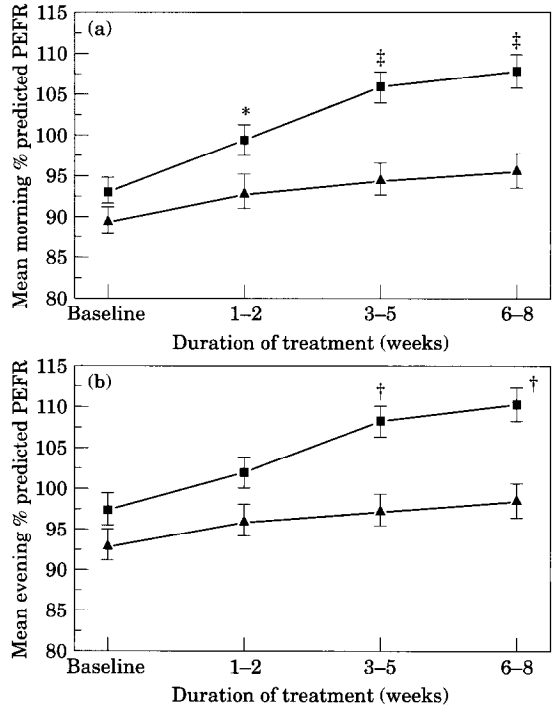

Fig. 1 Mean PEFR (SE) expressed as % of predicted, (a) morning, (b) evening. ■, Fluticasone propionate ($n=110$); ▲, Sodium cromoglycate ($n=115$); *$P<0{\cdot}05$; †$P<0{\cdot}01$; ‡ $P<0{\cdot}0001$.

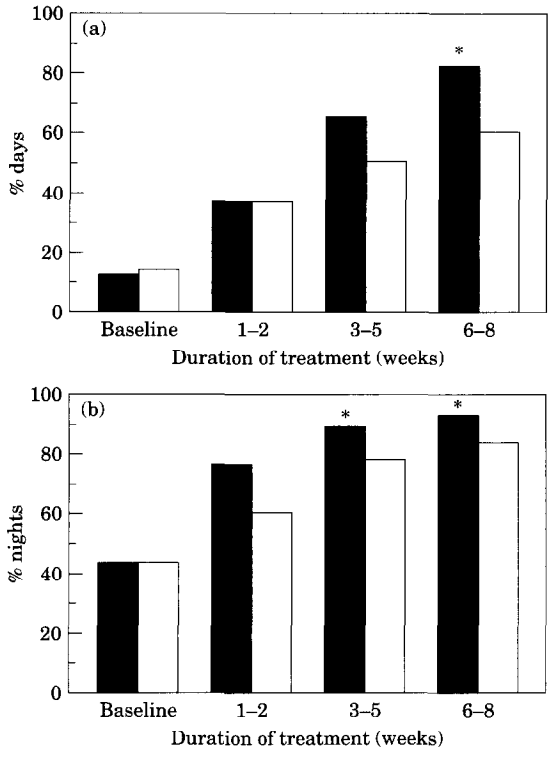

Fig. 2 Median percentage of symptom-free days (a) and nights (b) for each period of assessment during the study. Solid bar, fluticasone propionate; Open bar, sodium cromoglycate; *$P<0.05$.

79·1 (SD 16·3) to 87·8 (SD 16·6%) of predicted and with SCG, the increase was from 77·8 (SD 16·7) to 82·4 (SD 16·1)% of predicted. There was no evidence of a difference between treatments ($P=0.27$).

During the 2-week baseline period, the children had frequent symptoms and required bronchodilator treatment on most days. The median percentage of symptom-free days was about 15%, and symptom-free nights about 45%. The percentage of symptom-free days increased markedly on both treatments. The median percentages reached 84% with FP and 62% with SCG in the last 2 weeks. Symptom-free nights increased to 95% with FP and to 84% with SCG. There was a difference in favour of FP for the percentage of symptom-free nights at 3–5 weeks and at 6–8 weeks, and for the percentage of symptom-free days at 6–8 weeks (in all three cases, $P<0.05$). Point estimates suggest that this difference could represent at least two more symptom-free days and nights with FP than with SCG in the last 3 weeks of the treatment period (Fig. 2). The requirement for relief medication declined in both treatment groups with no obvious difference between the two (Table 2).

Table 2 Relief medication – mean number of doses of salbutamol

	Fluticasone propionate		Sodium cromoglycate	
	Day	Night	Day	Night
Baseline	1·97	0·50	1·91	0·61
Weeks 1–2	0·78	0·20	0·97	0·35
Weeks 3–5	0·60	0·14	0·74	0·28
Weeks 6–8	0·49	0·09	0·64	0·21

Table 3 Adverse events leading to withdrawal from the study

	Number of patients	
Adverse events	Fluticasone propionate ($n=110$)	Sodium cromoglycate ($n=115$)
Exacerbation of asthma	1	1
Acute chest pain	1	—
Breathless and wheeze	—	1
Burning sensation in chest	—	1
Sore threat	—	1
Stevens–Johnson syndrome	—	1
Medication-induced coughing	—	1
Medication-induced sickness	—	2
Unacceptable taste of medication	—	2
Total no. of patients who withdrew due to an adverse event	2	10

Of the 225 patients who entered the treatment period, 37 (16%) withdrew, 11 from the FP group and 26 from the SCG group. Twenty-five withdrew for reasons which appeared to be unrelated to the treatment. Two children taking FP and 10 children taking SCG withdrew because of adverse events (Table 3). Hoarse voice and oropharyngeal candidiasis were not observed in any of the children.

Discussion

Treatment with FP was superior to SCG for the primary variable, morning PEFR, and for the secondary variables of evening PEFR and symptom-free days and nights. The mean difference between treatments of 7·5% of predicted in morning PEFR is likely to be of clinical importance in terms of asthma management, as is an increase of 2 symptom-free days per 3 weeks. Additional analysis showed that

the improvement during treatment with SCG was significant (mean morning % predicted PEFR increased 7·8%; 95% CI 5·3–10·2; $P<0·0001$). However, the study was not placebo-controlled and some or all of the effect could be attributable to the 'clinical trial effect' (21). With a treatment period of 8 weeks, it is possible that neither therapy had reached its maximal effect, but there was no indication from the data that a longer treatment period would have changed the direction of the treatment difference.

For practical reasons, the study was conducted in an open fashion. As the two drug treatments look very different and the frequency of administration varies, the only way to make the study blind would have been to use a double dummy technique. The requirement for the children to take two separate inhaled treatments would probably have affected both recruitment and compliance. The 'clinical trial effect' was likely to have been similar with both treatments since these children had never received regular inhaled medication before, so both would represent a 'new' form of therapy. The primary variable was an objective measure of lung function. The statistical analysis was done by a department who had no clinical involvement with the patients, and assessed by an independent university statistics department.

Compliance with treatment could have influenced the results. It has been shown that compliance with four times a day administration is poorer than compliance with twice daily administration of inhaled therapy. On the basis of recorded medication use in diary cards during treatment, 23 patients (20 SCG:3 FP) were judged to have taken less than 75% and one patient (FP) to have taken more than 125% of their medication. Four other patients (two in each group) failed to record use of medication. When the data for morning and evening PEFR were re-analysed as per-protocol analyses, excluding these 28 patients, there was still strong evidence of a treatment difference in favour of FP. At weeks 6–8, the treatment difference in mean morning PEFR expressed as % predicted was 7·0% points in favour of FP (99% CI 1·1–12·8; $P=0·0022$). Similarly, for evening PEFR, the treatment difference was 5·6% points in favour of FP (99% CI 1·2–10·0; $P=0·0011$).

Recruitment to the study was aimed at children with mild–moderate asthma who were being considered for introduction of preventive therapy. No children entering the study had received SCG therapy or an inhaled corticosteroid in the past. It was notable, however, that the mean FEV_1 before entering the trial was less than 80% of predicted and, during the 2 weeks of pre-treatment assessment, many children were experiencing symptoms which required bronchodilator therapy on most days. This emphasizes the importance of daily evaluation of symptoms, and the use of objective measurement of lung function when deciding on the need for regular treatment.

Only a few small studies have compared SCG and inhaled corticosteroid treatment in childhood asthma. Three clinical trials comparing 4-week treatment periods and involving 40 children aged 7–15 years (7), 20 children aged 6–13 years (8) and 24 children aged 4–26 years (9) found an inhaled corticosteroid (betamethasone valerate or beclomethasone dipropionate) to be superior to SCG in terms of wheeze-free days and peak-flow rates recorded at home. The doses of inhaled corticosteroid used in these studies, ranging from 400–800 $\mu g\ day^{-1}$, were much larger than that used in the present trial. The dose of FP given in this study corresponds to beclomethasone 200 $\mu g\ day^{-1}$ (22). One trial did not detect any difference in efficacy between SCG and beclomethasone dipropionate but the power to detect a difference was low because numbers were so small (14 subjects aged 5–15 years) (10). Two further studies in children with severe asthma suggested that substitution of an inhaled corticosteroid improves asthma in children who respond inadequately to treatment with SCG (11,12). At the time these studies were done, there was no long-term experience of the use of inhaled corticosteroids in children and their use was largely confined to school-age children with severe asthma. It has since been shown that at these higher doses, it is possible to demonstrate some systemic effect on HPA axis (1–3). In a more recent study, Kraemer *et al.* found a greater improvement in lung mechanics and in non-specific bronchial reactivity in children given 100–200 μg beclomethasone dipropionate three times daily, compared with those given 20 mg SCG three times daily for 8 weeks (13). None of the published studies have addressed the question of the relative speed of action of the drugs. It is interesting that in the present study there was evidence of a difference in treatment effect in favour of FP for morning PEFR during the first 2 weeks of the treatment period (Fig. 1a).

No clinically serious, adverse events were reported with either drug but events resulting in withdrawal from the study were more frequent with SCG than with FP. Most of the adverse events were respiratory and seemed to indicate poor asthma control. Five children complained of retching, vomiting or an unpleasant taste after taking SCG by capsule powder device. The study period was short and no formal

assessment was made of adrenal axis function in the children taking FP. Studies of much longer duration with this new inhaled corticosteroid are needed before considering a change in the current recommendations for regular inhaled corticosteroid therapy in children with mild–moderate asthma. Nevertheless, the favourable results with FP in terms of efficacy and tolerability suggest that, in due course, it may be appropriate to lower the threshold for the administration of this inhaled corticosteroid to children, both in terms of age and severity of symptoms.

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